IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No. 10/664,991	Customer No. 23379
Applicant: Bjeldanes et al.	Confirmation No. 4613
Filed: Sep 16, 2003	Group Art Unit: 1614
Docket No. B03-074-1	Examiner: Betton, Timothy E

Title: *3,3'-Diindolylmethane Antiandrogenic Compositions*

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

We appeal from the Examiner's Feb 21, 2008 final rejections of claims 1-7 and 15-19.

REAL PARTY IN INTEREST

The real party in interest is the Regents of the University of California, the assignee of this application.

RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any other related appeals or interferences.

STATUS OF CLAIMS

Claims 1-7 and 15-19 are subject to this appeal; claims 8-14 and 20-22 are withdrawn by the Examiner from consideration.

STATUS OF AMENDMENTS

No after-final Amendment was filed; all Amendments are believed to be properly before the Board.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter is a method of providing an antiandrogen to a host determined to be in need thereof, the method comprising the steps of: (a) contacting the host with an effective amount of an antiandrogenic, optionally substituted 3,3'-diindolylmethane (DIM); and (b) detecting a resultant antiandrogenic response in the host. Specification, p.2, lines 18-21; claim 1.

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

I. DOES THE ACTION ESTABLISH THAT CLAIMS 1-7 AND 15-19 ARE UNPATENTABLE OVER NACHSCHON-KEDMI ET AL. (FOOD AND CHEMICAL TOXICOLOGY 41, 2003, 745-52) IN VIEW OF SAFE (US2002/0115708)?

ARGUMENT

I. THE ACTION DOES NOT ESTABLISH THAT CLAIMS 1 AND 4 ARE UNPATENTABLE OVER NACHSCHON-KEDMI ET AL. (FOOD AND CHEMICAL TOXICOLOGY 41, 2003, 745-52) IN VIEW OF SAFE (US2002/0115708).

As confirmed in the Declaration under 37CFR1.131, of record and attached hereto, the primary reference, Nachschon-Kedmi, is not applicable prior art. In particular, the present inventors invented the claimed subject matter prior to Nachschon-Kedmi's Jun 2003 publication.

The evidence is not limited to a single species: while the inventors' abstract attached to and referenced in the Declaration discloses that diindolylmethane (DIM) is a strong androgen antagonist attached, the inventors' also attached and referenced their "DISCLOSURE AND RECORD OF INVENTION FORM", which expressly refers to "DIM and more active derivatives"; in any event, claims 15-19 are limited to the use of diindolylmethane (DIM).

The secondary reference, Safe, teaches that DIM can inhibit the proliferation of androgen-independent cells (Specification, p.2, lines 6-7). Safe reports that in an androgen-insensitive prostate cell line (22Rv1), DIM is a weak inducer of a cytochrome P450 enzymatic activity (EROD) and an antagonist of the induction of this activity by the environmental contaminant TCDD; and that DIM can inhibit the proliferation of two androgen-insensitive prostate cells lines (22Rv1 and PC3, the latter do not even express androgen receptor). There is nothing in this secondary reference suggesting DIM is an antiandrogen; in fact, it was the present inventors who first made (and disclosed in the subject application) the surprising discovery that DIM is a potent antiandrogen. Specification, p.2, lines 10-12.

Appellants respectfully request reversal of the rejection.

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP
/richard aron osman/
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Mission Statement, USPTO External Customer Services Guide

CLAIMS APPENDIX

1. A method of providing an antiandrogen to a host determined to be in need thereof, the method comprising the steps of:

contacting the host with an effective amount of an antiandrogenic, optionally substituted 3,3'-diindolylmethane (DIM); and

detecting a resultant antiandrogenic response in the host.

2. The method of claim 1 wherein the method further comprises, prior to the contacting step, determining that the host is in need of the antiandrogen.

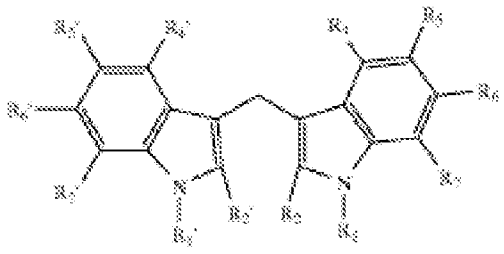
3. The method of claim 1 wherein the host is a human patient determined to be subject or predisposed to an androgen-dependent pathology, and the resultant antiandrogenic response is a reduction in the pathology or progress of the pathology.

4. The method of claim 1 wherein the host is a human patient determined to be subject or predisposed to an androgen-dependent pathology selected from the group consisting of prostate hyperplasia, acne, androgenetic alopecia and hirsutism, and the resultant antiandrogenic response is a reduction in the pathology or progress of the pathology.

5. The method of claim 4 wherein the patient is determined to be subject to prostate cancer.

6. The method of claim 4 wherein the patient is determined to be predisposed to prostate cancer.

7. The method of claim 1 wherein the optionally substituted 3,3'-diindolylmethane has the formula:



where R.sub.1, R.sub.2, R.sub.4, R.sub.5, R.sub.6, R.sub.7, R.sub.1', R.sub.2', R.sub.4', R.sub.5', R.sub.6' and R.sub.7' individually and independently, are hydrogen or a substituent selected from the group consisting of a halogen, a hydroxyl, a linear or branched alkyl or alkoxy group of one to ten carbons, and a nitro group.

8. (withdrawn) The method of claim 7 wherein R.sub.1, R.sub.2, R.sub.4, R.sub.5, R.sub.6, R.sub.7, R.sub.1', R.sub.2', R.sub.4', R.sub.5', R.sub.6' and R.sub.7' include a substituent selected from the group consisting of a halogen, a hydroxyl, a linear or branched alkyl or alkoxy group of one to ten carbons, and a nitro group.

9. (withdrawn) The method of claim 8 wherein the linear or branched alkyl or alkoxy group is one to five carbons.

10. (withdrawn) The method of claim 8 wherein the halogen is selected from the group consisting of chlorine, bromine and fluorine.

11. (withdrawn) The method of claim 8, wherein R.sub.1, R.sub.2, R.sub.4, R.sub.6, R.sub.7, R.sub.1', R.sub.2', R.sub.4', R.sub.6', and R.sub.7' are hydrogen, and R.sub.5 and R.sub.5' are a halogen.

12. (withdrawn) The method of claim 8, wherein R.sub.2, R.sub.4, R.sub.5, R.sub.6, R.sub.7, R.sub. 2', R.sub.4', R.sub.5', R.sub.6', and R.sub.7' are hydrogen, and R.sub.1 and R.sub.1' are an alkyl or alkoxyl having from one to ten carbons.

13. (withdrawn) The method of claim 8, wherein R.sub.1, R.sub.4, R.sub.5, R.sub.6, R.sub.7, R.sub.1', R.sub.4', R.sub.5', R.sub.6', and R.sub.7' are hydrogen, and R.sub.2 and R.sub.2' are an alkyl of one to ten carbons.

14. (withdrawn) The method of claim 8, wherein R.sub.1, R.sub.2, R.sub.4, R.sub.6, R.sub.7, R.sub.1', R.sub.2', R.sub.4', R.sub.6', and R.sub.7' are hydrogen, and R.sub.5 and R.sub.5' are nitro.

15. The method of claim 1 wherein the optionally substituted 3,3'-diindolylmethane is 3,3'-diindolylmethane.

16. The method of claim 3 wherein the optionally substituted 3,3'-diindolylmethane is 3,3'-diindolylmethane.

17. The method of claim 4 wherein the optionally substituted 3,3'-diindolylmethane is 3,3'-diindolylmethane.

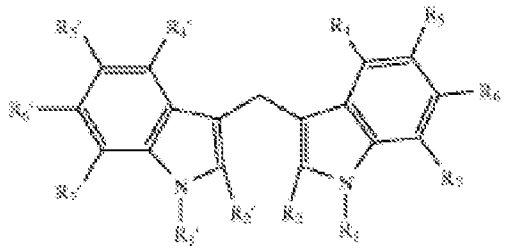
18. The method of claim 5 wherein the optionally substituted 3,3'-diindolylmethane is 3,3'-diindolylmethane.

19. The method of claim 6 wherein the optionally substituted 3,3'-diindolylmethane is 3,3'-diindolylmethane.

20. (withdrawn) The method of claim 4 wherein the optionally substituted 3,3'-diindolylmethane is perfluoro-3,3'-diindolylmethane.

21. (withdrawn) The method of claim 5 wherein the optionally substituted 3,3'-diindolylmethane is perfluoro-3,3'-diindolylmethane.

22. (withdrawn) The method of claim 6 wherein the optionally substituted 3,3'-diindolylmethane is perfluoro-3,3'-diindolylmethane.



RELATED PROCEEDINGS APPENDIX

No decisions in any related proceedings are known to exist.

EVIDENCE APPENDIX

The following relied-upon evidence of record is appended below:

1. Declaration under 37CFR1.131 by all the inventors, signed Sep 4 and 7, 2007, including attachments; provided with our Response dated Sep 8, 2007; entered and considered by the Final Action dated Feb 21, 2008.

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Title: *3,3'-Diindolylmethane Antiandrogenic Compositions*

DECLARATION UNDER 37CFR1.131

1. We are the coinventors of this patent application.

2. We invented the claimed subject matter prior to Jun 2003, as documented in the attached:
(i) abstract of our publication "Plant derived 3,3'-diindolylmethane is a strong androgen antagonist in human prostate cancer cells", J Biol Chem 2003 Mar 27 [epub ahead of print]; and
(ii) first three pages of our Disclosure and Record of Invention Form, signed Mar 31, 2003 and Apr 7, 2003.

3. Between Mar 27, 2003 and the Sep 16, 2003 filing date of the subject application we were diligent in preparing, reviewing, revising and filing this patent application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application and any patent issuing therefrom.

Date: 9/4/07 — Leonard F. Bjeldanes

Date: 9/7/07 — Gary L. Firestone

Date: 09/07/07 — Hien T. Le

1: J Biol Chem. 2003 Jun 6;278(23):21136-45. Epub 2003 Mar 27.

Plant-derived 3,3'-Diindolylmethane is a strong androgen antagonist in human prostate cancer cells.

Le HT, Schaldach CM, Firestone GL, Bjeldanes LF.

Department of Nutritional Sciences and Toxicology, The University of California, Berkeley, California 94720-3104, USA. lfb@nature.berkeley.edu

3,3'-Diindolylmethane (DIM) is a major digestive product of indole-3-carbinol, a potential anticancer component of cruciferous vegetables. Our results indicate that DIM exhibits potent antiproliferative and antiandrogenic properties in androgen-dependent human prostate cancer cells. DIM suppresses cell proliferation of LNCaP cells and inhibits dihydrotestosterone (DHT) stimulation of DNA synthesis. These activities were not produced in androgen-independent PC-3 cells. Moreover, DIM inhibited endogenous PSA transcription and reduced intracellular and secreted PSA protein levels induced by DHT in LNCaP cells. Also, DIM inhibited, in a concentration-dependent manner, the DHT-induced expression of a prostate-specific antigen promoter-regulated reporter gene construct in transiently transfected LNCaP cells. Similar effects of DIM were observed in PC-3 cells only when these cells were co-transfected with a wild-type androgen receptor expression plasmid. Using fluorescence imaging with green fluorescent protein androgen receptor and Western blot analysis, we demonstrated that DIM inhibited androgen-induced androgen receptor (AR) translocation into the nucleus. Results of receptor binding assays indicated further that DIM is a strong competitive inhibitor of DHT binding to the AR. Results of structural modeling studies showed that DIM is remarkably similar in conformational geometry and surface charge distribution to an established synthetic AR antagonist, although the atomic compositions of the two substances are quite different. Taken together with our published reports of the estrogen agonist activities of DIM, the present results establish DIM as a unique bifunctional hormone disrupter. To our knowledge, DIM is the first example of a pure androgen receptor antagonist from plants.

PMID: 12665522 [PubMed - indexed for MEDLINE]

Licensing Officer	UNIVERSITY OF CALIFORNIA, BERKELEY OFFICE OF TECHNOLOGY LICENSING **DISCLOSURE AND RECORD OF INVENTION FORM** (please read instructions and complete all pages)	B03-074 Case Number
Date Assigned		Class Code

Note: When completed, the Disclosure and Record of Invention Form is an important legal document. Care should be taken in its preparation. Please refer to accompanying instructions. If you need assistance, call the Office of Technology Licensing (UC Berkeley Patent Office) at (510) 643-7201. Information contained in this document is maintained in confidence by the the Office of Technology Licensing and normally will not be released to others except with attorney-client privilege, to research sponsors as required by contract, or under appropriate secrecy agreements, until a patent application is filed, the information is published, a determination not to file a patent application is made, or as may be required by law. The information contained should not be disclosed to others outside the University, except as described in section 4(f.), without the approval of the Office of Technology Licensing.

1. Title of Invention:

Indole-3-carbinol and 3,3'-diindolymethane, and derivatives, as antiandrogenic and prostate cancer therapeutic and protective agents.

2. A. Brief Summary of Invention (include novel features and advantages. Use additional sheets if necessary.)

Indole-3-carbinol (I3C) and its derivative, 3,3'-diindolylmethane (DIM), are natural compounds present in cruciferous vegetables. Our continuing studies of the cancer protective effects of these substances have shown that I3C and DIM inhibit the proliferation of androgen sensitive prostate tumor cells by different mechanisms. I3C blocks cell proliferation by a process that involves the selective inhibition of expression of cyclin-dependent kinase 6 (CDK6) protein and transcripts, and stimulated production of the p16 CDK inhibitor protein. DIM, however, can affect prostate tumor cell growth by at least two mechanisms. We have shown that DIM can bind to and block the activity of the androgen receptor (AR), and that DIM can activate the estrogen receptor (ER) by a process that does not involve binding to the receptor. There is considerable evidence in the literature that the combination of AR inhibition and ER activation is of crucial importance in the control of prostate tumorigenesis. Thus, DIM is the first example of a substance that is both a pure AR antagonist and an ER agonist. Because of their multiple antiproliferative mechanisms, the use of I3C and DIM, and more active derivatives, hold great promise for the control of prostate cancer.

B. Detailed Description of Invention (attach additional single-sided sheets)

Identify any references, patent applications, or other publications of which you are aware and which you believe to be pertinent to this invention. Please attach a copy of each of these references, if available.

(see attachment)

3. A. Funding Source/Sponsor — Contract/Grant No.(s) — Principal Investigator

(NOTE: IT IS EXTREMELY IMPORTANT THAT THIS SECTION IS COMPLETED)

see under disclosure sheet. -Beni

~~California Cancer Research Project — sc#09147V-10010 — PI - L.F. Bjeldanes~~

~~National Institute of Environmental Health Sciences Center — Grant P30-ES01896 — PI - L.F. Bjeldanes~~

B. This invention utilized data or materials from (check as many as apply):

( ) Celera's proprietary database
( ) Affymetrix chips
( ) A Material Transfer Agreement – "MTA" – (non-UC material)
( ) Other proprietary sources: specify_____).

4. Events For subject invention, what was the:	Date	Comments/References
a. Date of first conception of idea	May 1999	
b. Date of first description of complete invention, oral or written conception: identify document, page numbers and location of document	March 2003	
c. Date of first successful demonstration of reduction to practice of invention	Not yet used in practice	
d. Date of first publication containing full description of invention (very important – establishes bar date)	DIM publication in press in JBC – on line 4/1/03 I3C publication in preparation	
e. Dates of external oral disclosures to non-UC employees		
f. Date of planned submission of report, paper, thesis describing invention		

5. If any proprietary material (e.g., cel. e, antibody, plasmid, computer software, chemical compound) obtained from outside your laboratory was used to develop this invention under a restrictive written or oral transfer agreement (other than a normal purchasing agreement), please attach a copy or summary of that agreement.

6. INVENTOR INFORMATION. Note: Please fill out completely to allow for timely and accurate distribution of royalty income (to add more inventors go to page 3).

Leonard F. Bjeldanes 3/31/03	3/31/03
Signature / Date	Signature / Date
Leonard F. Bjeldanes / Professor	Gary L. Firestone / Professor
Print name / Title	Print name / Title
Nutritional Sciences and Toxicology	Molecular and Cell Biology
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Home Address	Home Address
United States of America	U.S.A.
Country of Citizenship (required for patenting)	Country of Citizenship (required for patenting)

ADD ADDITIONAL INVENTORS ON FOLLOWING PAGES ----------->

7. For any Inventor named (item 6, above) who is not employed full-time by the University of California, please identify other employers (e.g., Veterans Administration, Howard Hughes Medical Institute, USDA), the percent of salary time funded by such other employer, and the nature of the other employment (such as research, teaching or clinical duties).

8. Technically Qualified Witnesses (Two Required) - invention disclosed to and understood by:

3/31/03	3/31/03
Signature / Date	Signature / Date
JOSEPH L. NAPOLI	SHARON FLEMING
Print name	Print name

Please submit this form with original signatures to:

Director
Office of Technology Licensing
2150 Shattuck Avenue, Suite 510, MC 1620
Berkeley, CA 94720-1620

INVENTOR INFORMATION (CON NUED FROM PAGE 2). Note: Pleas. .ll out completely to allow for timely and accurate distribution of royalty income.

Hien Le — Signature
04/07/03 — Date
Hien Le — Print name
Ph.D. — Title
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City State Zip
Telephone No. (Office/Lab) Fax No.
8916 Libra Drive, San Diego, CA 92126, — Home Address
U.S.A. — Country of Citizenship (required for patenting)

Signature Date
Print name Title
Dept./ORU (required for income distribution) (or Employer if not UC)
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e-mail address
City State Zip
Telephone No. (Office/Lab) Fax No.
Home Address
Country of Citizenship (required for patenting)

Signature Date
Print name Title
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e-mail address
City State Zip
Telephone No. (Office/Lab) Fax No.

Signature Date
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e-mail address
City State Zip
Telephone No. (Office/Lab) Fax No.